

U.S.S.N. 10/014,149

Filed December 19, 2001

**SUPPLEMENTAL AMENDMENT AND RESPONSE TO OFFICE ACTION****Remarks**

The applicants and the undersigned greatly appreciate the courtesy of the examiner in extending an opportunity to discuss the claimed invention, the clinical data in support of the data, and why the prior art is different and fails to make obvious the claimed method of treatment.

**Amendments to the Claims**

The title has been amended to reflect the scope of claims in this application following the restriction requirement. As discussed at the interview, the claims have been narrowed to define administration of a composition comprising only milnacipran as the active ingredient to treat the pain and fatigue associated with fibromyalgia. The combination claims will be pursued in a continuation application.

**Rejection Under 35 U.S.C. § 103**

Claims 1-9 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Nagaoka, et al., *Medicine and Drug Journal* 37(10):238-240 (2001) ("Nagaoka") or (WO 01/26623) to Horrobin et al. ("Horrobin"), in view of U.S. Patent No. 6,395,788 to Iglehart III ("Iglehart") or (WO 00/56310) to Mendel et al. ("Mendel"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended and in view of the accompanying Declaration under 37 C.F.R. 1.131.

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**SUPPLEMENTAL AMENDMENT AND RESPONSE TO OFFICE ACTION***The Prior Art***Horrobin**

Horrobin corresponds to U.S. Patent No. 6,441,038. Both the PCT application and U.S. patent are referred to jointly herein as "Horrobin". Horrobin describes the treatment of fatigue, associated with various neurological insults, by the use of agents which increase norepinephrine levels in the brain (specifically via reuptake inhibition), in combination with amino acids that provide the precursors to maximize this effect.

Three different monoamine neurotransmitters are present within the human brain: noradrenaline (NE; also referred to as norepinephrine), dopamine, and serotonin (5-HT). ("Monoamine" refers to a particular chemical structure typically derived from an amino acid.) Both NE and 5-HT are involved in the regulation of mood and pain perception. Dopamine has critical roles in movement and in motivation; it also plays a minor role in mood regulation. Both dopamine and NE are derived from the precursor amino acid phenylalanine (the synthetic pathway is shown in figure 1) while 5-HT is derived from a separate amino acid, tryptophan.

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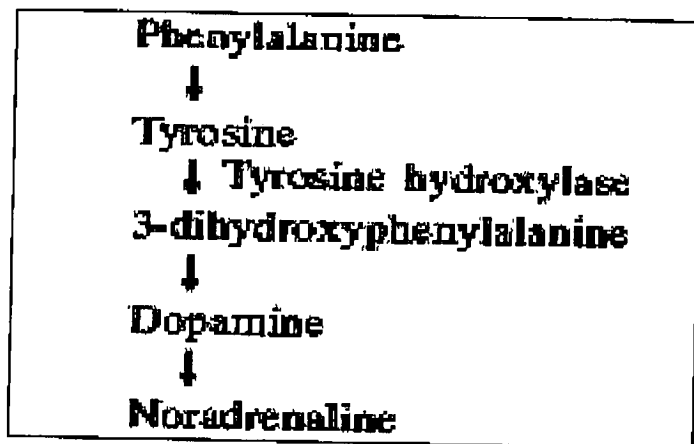


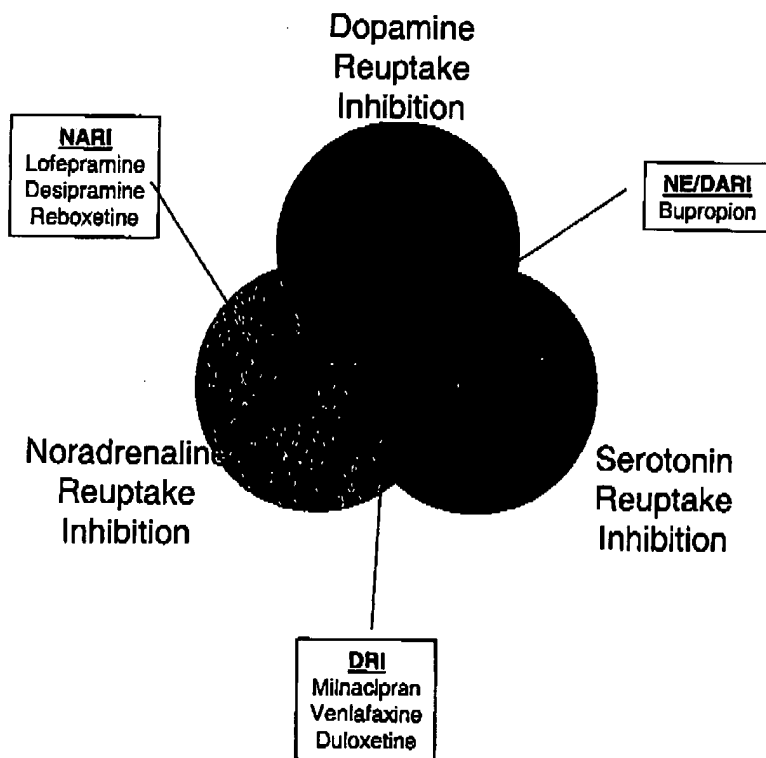
Figure 1

Horrobin et al. focus on the class of agents known as NARI's (NE reuptake inhibitors, including lofepramine, desipramine, and reboxetine (See Figure 2) for the treatment of fatigue. In his paradigm, treating fatigue is solely dependent upon increasing brain norepinephrine concentrations. While he referenced dual serotonin-norepinehrine reuptake inhibitors (DRI's, including milnacipran, venlafaxine, and duloxetine), their inclusion is predicated by the fact that they have some noradrenergic reuptake activity. Critical to the Horrobin method of treatment, is the disclosure that both NARI and DRI compounds are ineffective in treating fatigue when used alone. Rather, efficacy requires that such compounds be supplemented by an amino acid NE precursor, such as phenylalanine or tyrosine. Mechanistically, Horrobin teaches that higher synaptic concentrations of noradrenaline can be achieved by increasing production by both providing a noradrenaline precursor and by blocking its subsequent reuptake.

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**Figure 2**

Case History #1 in Horrobin's specification is particularly relevant, as it describes a patient suffering from fibromyalgia. The patient had been treated with a variety of drugs, including tricyclic antidepressants (which can be DRIs, NARIs, or 5-HT reuptake inhibitors), "serotonin reuptake inhibiting and norepinephrine reuptake inhibiting antidepressants," and NSAIDs, without efficacy. However, when the NARI lofepramine is coadministered with phenylalanine, efficacy is achieved.

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The claimed method of treatment differs from Horrobin et al, in several respects (Table 1). First, and most critical, the claimed method is specific to milnacipran (or an agent with similar pharmacology vis a vis 5-HT and NE) as an effective therapy when used alone without any amino acid supplementation. Horrobin et al teaches specifically away from such monotherapy being effective. Second, the therapeutic goal in the claimed method is to treat both the pain and fatigue associated with fibromyalgia, rather than fatigue alone. The claimed treatment is predicated on the requirement for activity against both NE and 5-HT (specifically, NE > 5-HT), as efficacy is not achieved by 5-HT specific agents, NARI compounds, or even by DRIs that preferentially block the reuptake of 5-HT (See Table 2).

**Table 1**

	<b>Horrobin</b>	<b>149 + 547</b>
Effective Composition	<u>Combination</u> of NARI or SNRI + phenylalanine or tyrosine	DRI (specifically NE > 5-HT) in isolation
Preferred Embodiment	Lofepramine (NARI) + phenylalanine	Milnacipran
Symptoms Treated	Fatigue	Pain + fatigue

**Mendel**

Mendel teaches the use of N, N,-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine-HCl (sibutramine), and closely related cyclobutyl compounds for treating fatigue. Mendel teaches that sibutramine inhibits reuptake of all three monoamines (5-HT, NA, and DA). Mendel does not teach a serotonin-noradrenaline reuptake inhibitor. Further,

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milnacipran is an unrelated *cyclopropyl* based compound. Mendel does not teach a single compound with the chemical structure of Milnacipran for treating CFS.

**Iglehart**

Iglehart discloses the use of cyclobenzaprine (a 5-HT<sub>2</sub> receptor antagonist), optionally together with an SNRI, to treat sleep disturbances associated with fibromyalgia. Iglehart does not disclose or suggest the use of milnacipran to treat fibromyalgia or its symptoms. Iglehart does not disclose the use of any NSRI alone to treat fibromyalgia or its symptoms. Iglehart does not provide any motivation to modify the references of Nagaoka or Horrobin to derive the claimed method of treatment of fibromyalgia with milnacipran.

**Horrobin, Mendel and Iglehart in combination**

There is no teaching in the prior art that would suggest combining the references as applicants have done, to treat the pain or fatigue associated with fibromyalgia using just milnacipran. Horrobin does not disclose the use of milnacipran, or compounds with the same mechanism of action, alone in treating myalgia and instead teaches away from using milnacipran without phenylalanine or tyrosine. Mendel and Iglehart do not address these deficiencies nor do they provide the motivation to combine these references and then modify the result as applicants have done, with a reasonable expectation of success in treating pain and fatigue associated with fibromyalgia. One of skill in the art would not be motivated to combine these references and derive the present method for treating the chronic pain and fatigue associated with FMS by administering milnaciprin.

Table II

	Compound	Tradename	Norepinephrine (NE)	Serotonin (5-HT)	Efficacy in FMS
<b>SSRIs</b> Serotonin Specific Reuptake Inhibitors - almost pure 5-HT effect	Citalopram	Celexa <sup>TM</sup> (Forest Labs)	1	3300	MINIMAL
	Fluoxetine	Prozac <sup>TM</sup> (Lilly)	1	55	
<b>SNRIs</b> Serotonin Norepinephrine Reuptake Inhibitors -  Some NE, but still mostly 5-HT effect	Venlafaxine	Effexor <sup>TM</sup> (Wyeth)	1	30	MINIMAL
	Duloxetine	Cymbalta <sup>TM</sup> (Lilly-in development)	1	8	?
<b>TCAs</b> Tricyclic antidepressants - more NE than 5-HT activity	Amitriptyline	Elavil <sup>TM</sup> (Roche)	1.6	1	SIGNIFICANT
<b>NSRI</b> Norepinephrine Serotonin Reuptake Inhibitor - more NE than 5-HT activity	Milnacipran	Ixel <sup>TM</sup>	3.3	1	SIGNIFICANT
<b>NARI</b> Selective Norepinephrine Reuptake Inhibitor  Some 5-HT, but mostly NE effect	Reboxetine	Edronax (Europe)	50	1	?
	Nortriptyline	Pamelor	200	1	MINIMAL

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Nagaoka

Enclosed is a Declaration under 37 C.F.R. 1.131 which shows conception prior to publication of Nagaoka, in October 2001, followed by diligent reduction to practice by filing of the parent application, U.S.S.N. 10/014,149 on November 5, 2001. This removes Nagaoka as a prior art reference.

Allowance of claims 1-9 and 31-33 is respectfully solicited.

Respectfully submitted,



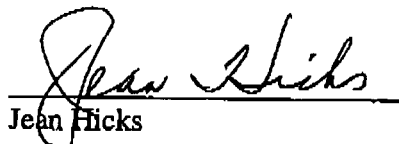
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**Certificate of Facsimile Transmission**

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, March 6, 2003, to the Commissioner for Patents, U.S. Patent and Trademark Office, Washington, DC 20231.

  
Jean Hicks

Date: March 7, 2003



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Marked Up Version of Amended Claims

**Marked Up Version of Amended Claims**  
**Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)**

1. (Three times Amended) A method of treating fibromyalgia syndrome (FMS) comprising administering to an animal subject suffering from FMS, a composition [comprising as] wherein the active ingredient consists of milnacipran, or a pharmaceutically acceptable salt thereof in an amount effective to treat the chronic pain and fatigue associated with FMS.

Claims 2-6 have been cancelled.

7. The method according to claim 1, wherein the animal subject is human.

8. (amended) The method according to claim 1, wherein the amount of milnacipran administered is from about 25 mg to about 400 mg per day.

9. The method according to claim 1, wherein the milnacipran is formulated in a sustained release formulation.

Claims 9-30 have been cancelled.

31. The method of claim 1 wherein the amount of milnacipran administered is at least 100 mg per day.

32. The method of claim 1 wherein the amount of milnacipran administered is between 100 and 400 mg per day.

33. The method of claim 1 wherein the amount of milnacipran administered is between 100 and 250 mg per day.